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Biosafety risk assessment and risk control of clinical laboratory in designated hospitals for treating COVID-19 in Chongqing, China

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The authors declare no competing interests.

Highlights

- There are few reports on the biosafety risk assessment and biosafety risk control of other laboratory tests except for nucleic acid testing during the treatment of COVID-19 patients.
- In our manuscript, we emphasized the importance of risk monitoring for continuous improvement of risk management following biosafety risk assessment and biosafety risk control.
- We proposed that laboratory management should formulate appropriate but not excessive control measures when conducting biosafety risk control, and should consider whether the control measures will bring about cross-contamination of the test.

Abstract

Background

If a nucleic acid preservation solution containing viral inactivators is used, the biosafety risk in the process of detecting the nucleic acid of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) will be low. Patients infected with SARS-CoV-2 are sent to designated hospitals for treatment in China, except for detecting nucleic acid of SARS-CoV-2, other laboratory tests such as bacterial culture may also be carried out while the patients are being treated. However, in addition to nucleic acid testing, biosafety risks in the testing of these items for patients with coronavirus disease 2019 (COVID-19) might be ignored. Therefore, we identified and evaluated risks in these detection processes and formulated appropriate, but not excessive control measures for biosafety risk, to improve the work efficiency and prevent biosafety accidents.

Methods

Biosafety risks in all laboratory tests for COVID-19 patients were identified and evaluated according to the risk severity and occurrence probability. Subsequently, the corresponding control measures for biosafety risk were formulated according to the identified risk. Hereafter, risk monitoring was carried out.

Results

More than 32 risks in the entire laboratory testing process were identified and evaluated, and the residual risk after the implementation of the control measures was acceptable.

Conclusion

The biosafety risk assessment of laboratories in designated hospitals for treating COVID-19 should be re-implemented before testing specimens for COVID-19 patients. Risk management by risk monitoring is even more important, as it can prevent the occurrence of biosafety incidents and can continuously improve risk management.

Keywords

COVID-19; designated hospital; laboratory biosafety; risk assessment; risk control

Introduction

The outbreak of coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) at the end of 2019 has become a global pandemic.[1] Chinese health authorities have adopted a series of effective measures, including nucleic acid testing of SARS-CoV-2 among large-scale populations and the timely and effective diagnosis and treatment of COVID-19, which has played a key role in the control of the epidemic in China.[2,3] Nevertheless, in the early stages of the epidemic, multiple occupational exposure incidents involving laboratory personnel occurred in medical laboratories in China. The main reason was that the laboratory management was not aware of the changes in the pathogenic microorganisms exposed during the test activities at the beginning of the epidemic,[4] laboratory personnel might be exposed to a novel then-unknown virus, which was subsequently named SARS-CoV-2. However, they still used the original control measures for biosafety risk, which could not control the biosafety risk posed by SARS-CoV-2. A few months after the outbreak, viral inactivators such as guanidine salts and nucleic acid lysates were contained in nucleic acid preservation solutions in China, therefore,

the risk of nucleic acid testing of SARS-CoV-2 was significantly reduced. In contrast, because the sputum, fecal, and blood samples of COVID-19 patients are not virus-inactivated before testing, there is a high biosafety risk in the process of testing these samples. It is worth noting that these risks can be easily ignored by laboratory personnel and management, resulting in infection among the laboratory personnel.[5] In contrast, some laboratories have taken inappropriate and excessive control measures for biosafety risk against the risk of nucleic acid testing for SARS-CoV-2. For example, in the area of specimen preparation and amplification, specimens and test waste must be autoclaved according to experts in China, which not only wastes limited medical resources and reduces the work efficiency, but also leads to cross-contamination of nucleic acid testing.

Therefore, it is necessary to conduct an objective and scientific biosafety risk assessment for test activities in the clinical laboratories of hospitals designated to treat COVID-19, and further, to formulate appropriate but not excessive control measures.

Chongqing is adjacent to Hubei Province, where the epidemic originated. Since the beginning of the epidemic, our hospital (Yongchuan Hospital of Chongqing Medical University) had been one of the designated hospitals for treating COVID-19 in Chongqing. In addition to nucleic acid testing for SARS-CoV-2, the department of medical laboratory medicine was also required to undertake other laboratory tests of patients with COVID-19. Notably, during the treatment of patients with COVID-19, there was no occupational exposure incident in our clinical laboratory, and there was no incidence of cross-contamination in nucleic acid testing. Therefore, we shared our lessons learned with professionals on biosafety risk assessment and risk management in the clinical laboratories of

designated hospitals for the treatment of patients with COVID-19.

Methods

In various clinical laboratory tests of patients with COVID-19, the potential risks involved with respect to laboratory personnel (training, competence, protection.), biosafety equipment and facilities, disinfectants, the testing process of various specimens, and laboratory waste are considered as the research objects of the biosafety risk assessment.

First, the characteristics of SARS-CoV-2 were understood, including the degree of hazards, biological characteristics, transmission and infection characteristics, virulence, stability in the environment, and prevention and diagnosis programs. Second, using the fishbone diagram method, the potential risks of the seven elements involved in the test activities were identified, evaluated, controlled, and monitored (as shown in Fig.1).

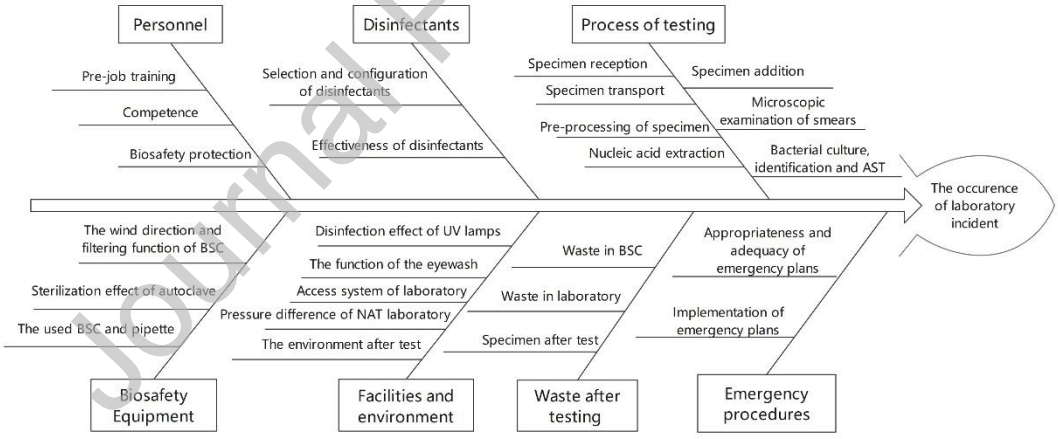

Fig.1 The fishbone diagram of risk identification.

BSC: biological safety cabinet; UV: ultraviolet; NAT: nucleic acid testing; AST: antimicrobial susceptibility test.

The acceptable range of biosafety risk should be determined before risk assessment by laboratory management; additionally, we considered a hazard level within 5 as the acceptable

range. A biosafety risk evaluation was carried out referring to the "Laboratory Biosafety Manual (Fourth Edition)" published by WHO,[6] which adopted the quantification procedure of hazard degree (hazard degree = severity × probability of occurrence) to quantify the hazard degree of each biosafety risk. The severity of the biosafety risk was divided into five levels: no harm, minor, moderate, major, and catastrophic, and was scored as 1, 2, 3, 4, and 5, respectively. The probability of occurrence was divided into five levels: impossible, uncommon, occasional, frequent, and inevitable, and was scored as 1, 2, 3, 4, and 5, respectively. Subsequently, it was compared with the established acceptable range to determine whether the risk was acceptable. For unacceptable risks, appropriate control measures for biosafety risk were formulated and implemented to minimize the risk from the two aspects of reducing risk severity and (or) probability of risk occurrence. The residual risk is subsequently evaluated as a whole to form a biosafety risk assessment report.

After the initial biosafety risk assessment was completed, we regularly maintained the risk management in our laboratory. As Chinese health authorities have successively announced the environmental stability and respiratory transmission route of SARS-CoV-2, and determined our hospital as one of the hospitals designated to treat COVID-19, we have initiated risk assessment several times on this basis. Additionally, we also monitored the exposure and infection of laboratory personnel by conducting daily nucleic acid testing for SARS-CoV-2. Cross-contamination was monitored by setting three negative controls in each batch of testing. Some methods were used to identify unidentified risks and evaluate the continuous suitability of control measures for biosafety risk, such as real-time dynamic monitoring of the changes in test activities and test specimens, monthly biosafety self-

inspection, annual biosafety risk review and analysis, and a summary of laboratory incidents. This was done to achieve the purpose of continuous improvement of biosafety risk management (The timeline is shown in Fig. 2).

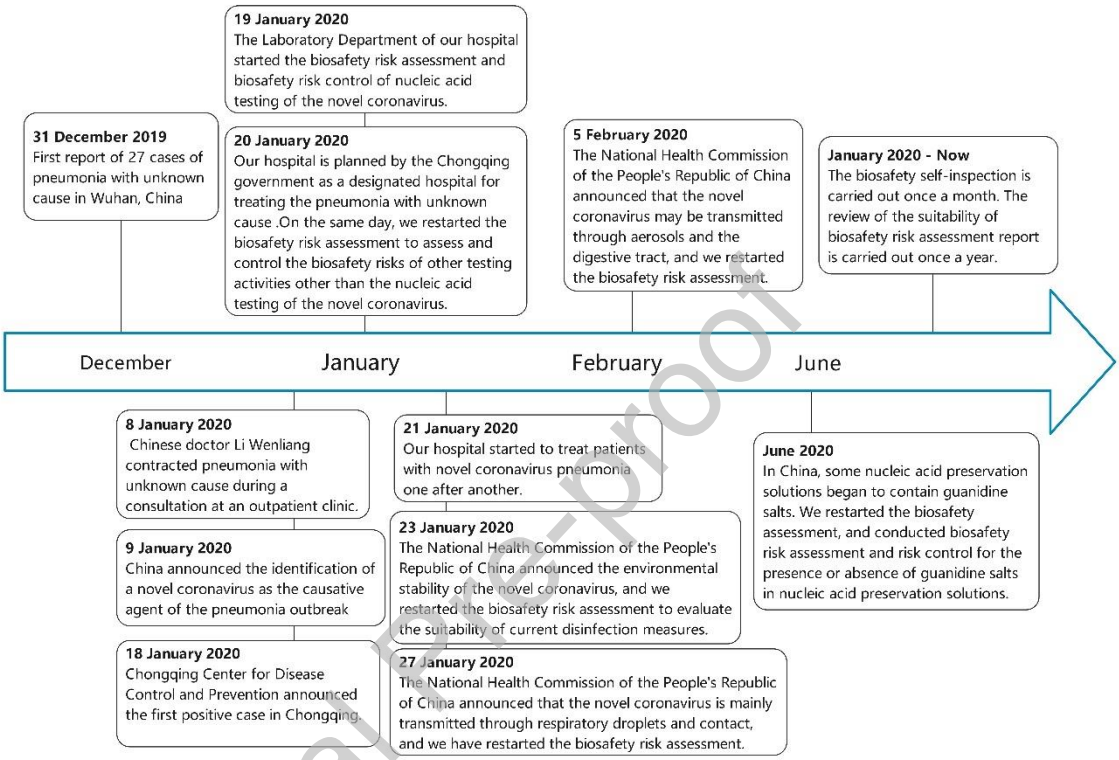

Fig. 2 Timeline for starting biosafety procedures

Results

Characteristics of SARS-CoV-2

SARS-CoV-2 is a pathogenic microorganism with a secondary hazard level and high transmissibility. Transmission occurs mainly through respiratory droplets and contact.[7] Current research has shown that the virus is sensitive to ultraviolet (UV) rays, heat, 75% alcohol, chlorine-containing disinfectants, hydrogen peroxide, diethyl ether, and other fatty solvents.[8] The virus can be inactivated by heating at 56 °C for 30 min[9]; however, it cannot be effectively inactivated by chlorhexidine.[10] Fever, fatigue, and dry cough are the most common symptoms of infection.[11] To date, effective vaccines and therapeutic drugs have been developed. [12,13]

Test activities carried out in the clinical laboratory

The test activities of clinical laboratories to be undertaken include specimen reception, specimen processing, specimen testing, waste disposal, etc. The types of specimens from patients with COVID-19 include upper respiratory, lower respiratory, blood, urine, body fluid, and fecal specimens. The test items for the patients in the clinical laboratory include clinical hematology testing, clinical body fluid (including feces) testing, clinical chemistry testing, clinical immunology testing, the microbial culture of respiratory specimens (including sputum), nucleic acid testing of SARS-CoV-2, and immune cell (CD3/CD4) testing.

We identified 32 risks in total, all of which had a hazard level greater than 5. Risk 1 existed in laboratory personnel, risks 2-4 existed in biosafety equipment, risks 5-6 existed in disinfectants, risks 7-11 existed in facilities and the environment, risks 12-25 existed in the process of laboratory tests, risks 26-30 existed in waste after testing, and risks 31-32 existed in emergency procedures. After formulating and implementing corresponding control measures for biosafety risk, the residual risks were within the acceptable range (Table 1, Table 2, and Table 3).

During the biosafety risk monitoring, no unidentified risks were identified. The established control measures for biosafety risk were appropriate and did not cause cross-contamination. Nearly several months after the initial biosafety risk assessment and biosafety risk control were implemented, the nucleic acid preservation solutions were changed from containing no viral inactivators to containing viral inactivators in China. So on conducting risk monitoring, we found that some biosafety risks we originally identified did not exist anymore, and the original protection measures for nucleic acid testing were excessive protection, including wearing N95 masks, double-layer latex gloves, goggles, shoe covers, isolation clothing, and protective clothing. After reassessing the risk, the protective measures were changed to wearing medical protective masks, single-layer gloves, goggles, isolation clothing, or protective clothing. (as noted with "△" in Table 1).

Potential risk number	Risk identification	Notes
1	Laboratory personnel are not trained in relevant biosafety knowledge or do not take appropriate protection when entering the laboratory for operation, resulting in the risk of environmental contamination, occupational exposure, or other people infected.	
2	There is a risk of personal infection or environmental contamination due to malfunction of the airflow or filtration of the biological safety cabinet (BSC).	
3	The BSC and the pipettes are not disinfected after use, resulting in the risk of personnel infection or environmental contamination.	
4	There is a risk of environmental contamination due to the malfunction of the autoclave and the disinfection effect is not achieved.	
5	The concentration of laboratory disinfectants is improperly selected and the disinfection effect is not achieved, resulting in the risk of environmental contamination, or personnel infection.	
6	The 75% alcohol or chlorine-containing disinfectant has been placed for too long, the concentration has decreased, and the disinfection effect has not been achieved, resulting in the risk of environmental contamination, or personnel infection.	
7	The intensity of the UV lamp does not meet the standard in the testing laboratory, resulting in the risk of personnel infection or environmental contamination.	
8	The eyewash device is malfunctioning and the eyes cannot be washed in time when occupational exposure occurs, resulting in the risk of personnel infection.	
9	The external personnel enter the laboratory by mistake, resulting in the risk of personnel infection.	
10	Air escape from the sample preparation room in the nucleic acid testing laboratory, resulting in the risk of contaminating other areas.	
11	The pressure difference between nucleic acid testing laboratories is abnormal, resulting in the risk of environmental contamination.	
12	The laboratory room is not disinfected after testing, resulting in the risk of personnel infection due to contaminated items or air.	
13	During the process of specimen reception, there is a risk that the personnel's hands are contaminated by the specimen tubes, which are contaminated during specimen collection.	
14	During the indoor transfer of respiratory specimens and fecal specimens, there is a risk of personnel infection.	
15	During the indoor transfer of respiratory specimens and fecal specimens, there is a risk of specimen spillage causing environmental contamination.	
16	During the process of operation in the BSC, there is a risk of contaminating the environment or items by hands contaminated when remove from the BSC.	
17	During the process of nucleic acid extraction, there is a risk of personnel infection or environmental contamination due to aerosols generated in the process of shaking.	△
18	During the process of nucleic acid extraction, there is a risk of specimen spillage causing the contamination of the countertop or gloves.	△
19	During the process of specimen centrifugation, there is a risk of personnel infection or environmental contamination due to the generated aerosols.	△
20	During the process of specimen addition, there is a risk of personnel infection due to generated aerosols.	
21	During the process of specimen addition, there is a risk of specimen spillage causing the contamination of the countertop or gloves.	△
22	During the testing process of fecal specimens, there is a risk of personnel infection due to the aerosols generated by smear and risk of environmental	

	contamination owing to specimen or laboratory wastes after testing being taken out of the laboratory without disposal.	
23	During the microscopic examination of fecal specimens, there is a risk of the lens and stage of the microscope being contaminated by the specimen.	
24	During the process of culture, the identification, and antimicrobial susceptibility test of respiratory specimens and fecal specimens, there is a risk of personnel infection due to aerosols generated by specimen addition or specimens splashing into the eyes.	
25	During the process of observing the colonies of bacterial cultures of respiratory specimens and fecal specimens, there is a risk of personnel infection due to aerosols.	
26	During the process of nucleic acid testing, there is a risk of environmental contamination owing to laboratory wastes in the BSC being taken out of the laboratory without disposal.	△
27	During the process of culture, identification, and antimicrobial susceptibility test of respiratory specimens and fecal specimens, there is a risk of personnel infection or environmental contamination owing to laboratory wastes in the BSC being taken out of the laboratory without disposal.	
28	During the process of nucleic acid testing, there is a risk of environmental contamination owing to laboratory wastes in the sample preparation room, specimens after testing, and personal protective equipment being taken out of the laboratory without disposal.	△
29	The specimen after the nucleic acid testing is lost, resulting in the risk of personnel infection or environmental contamination.	△
30	The respiratory specimen after the bacterial culture is lost, resulting in the risk of personnel infection or environmental contamination.	
31	During the formulation of the emergency procedures, the factors of biosafety risk are ignored or the emergency response measures are inappropriate, resulting in the risk of the occurrence of major or catastrophic biosafety incidents.	
32	When a biosafety incident occurs, the on-site personnel are not familiar with the disposal process in the emergency procedures, resulting in the risk of causing harm to the environment and human health.	

Notes：△ means that the risk does not exist if the specimen preservation solutions contain viral inactivators, such as guanidine salts or nucleic acid lysates.

Table 1. Identification of laboratory biosafety risks

Potential risk number	Severity	Probability	Hazard degree
1	5	4	20
2	4	2	8
3	4	3	12
4	4	2	8
5	4	3	12
6	4	4	16
7	3	3	9
8	4	4	16
9	4	3	12
10	4	3	12
11	4	2	8
12	3	3	9
13	5	4	20
14	4	4	16
15	4	3	12
16	5	4	20
17	5	5	25
18	4	3	12
19	4	5	20
20	4	4	16
21	4	4	16
22	4	4	16
23	4	4	16
24	4	5	20
25	4	5	20
26	4	3	12
27	4	3	12
28	4	3	12
29	5	3	15
30	4	4	16
31	5	4	20
32	4	3	12

Table 2. Evaluation of laboratory biosafety risks

Potential risk number	Control measures
1	The qualifications of the laboratory testing personnel should be stipulated. A system of training, examination, and authorization should be established. Before engaging in testing, the laboratory testing personnel should be re-trained in biosafety risk assessment, protection levels, procedures for putting on and taking off personal protective equipment, and emergency procedures. Only after passing the examination can they be authorized to engage in testing work.
2	A standard operating procedure (SOP) should be established for the BSC, including the maintenance, the periodic calibration of the BSC, user training, etc. The wind direction and filtering function of BSC should be monitored before use, the maintenance of BSC should be performed periodically and the calibration should be performed once a year.
3	An SOP should be established and it should be stipulated that 75% alcohol should be used to spray and disinfect the inner wall of the BSC and the pipette after each test.
4	An SOP should be established for the autoclave, including the maintenance, the periodic calibration of the autoclave, user training, etc. Physical and chemical monitoring should be carried out every time the autoclave is used, biological monitoring should be carried out once a month and the corresponding records should be completed. The maintenance of the autoclave and the calibration of the pressure valve and pressure gauge should be performed periodically.
5	An SOP should be established for laboratory disinfection. Various laboratory disinfectants and the corresponding appropriate concentrations should be stipulated. All the staff should be trained and assessed according to the SOP.
6	An SOP should be established for laboratory disinfection. Disinfectant concentrations should be periodically monitored and recorded to maintain the effectiveness of the disinfectant at all times.
7	A procedure, to monitor the UV intensity of UV lamps using UV indicator cards on a quarterly basis is established and implemented.
8	A maintenance procedure for eyewash devices should be established. The daily maintenance of water holes and water pressure should be carried out.
9	Laboratory access control devices should be set up, and biohazard signs should be posted on the door of the laboratory. An access system should be established, which stipulates that the external personnel who need to enter the laboratory should be approved by the laboratory director, be notified of risks, and be protected accordingly.
10	If it is designed to use natural ventilation, the transfer of items to the reagent preparation room and the amplification room should be passed through the interlocking transfer window with a UV disinfection function. An SOP for mechanical ventilation should be established, which stipulates that the transfer of items between the sample preparation room and the reagent preparation room, and the transfer of items between the sample preparation room and the amplification room must be passed through the transfer window, and after the items are placed in the transfer window, the window door should be closed, and subsequently, the UV lamp must be turned on. The UV lamp tube should be wiped and maintained every week, and the intensity of the UV lamp should be monitored quarterly.
11	Pressure monitoring gauges should be installed in each room and buffer room of the PCR laboratory. An SOP should be established for pressure monitoring, which stipulates that laboratory personnel should check whether the pressure is within the allowable range before entering the nucleic acid laboratory for operation.
12	An SOP for laboratory disinfection should be established. UV lamps should be installed in each room of the laboratory, the distance from the tabletop should not exceed 100 mm, and the disinfection process should be recorded. Alternatively, it can be disinfected with a mobile UV lamp.
13	An SOP for specimen reception should be established. The personnel who received specimens only take the biosafety protection at level 2, and all specimens must be

received in a BSC, including respiratory culture specimens, nucleic acid testing specimens, blood specimens, etc. Subsequently, the surface of the specimen tube should be disinfected by spraying with 0.2% chlorine-containing disinfectant. If the specimen tube leaks during the receiving process, firstly dry it with absorbent paper, subsequently spray and disinfect the surface of the specimen tube and the absorbent paper with 0.55% chlorine-containing disinfectant.[14] All the staff should be trained and assessed according to the SOP.

14 An SOP should be established for specimen transport, which stipulates that the specimen must be triple-packed for transport. All the staff should be trained and must follow the protocol.

15 An SOP for specimen transport, cleaning and disposal of specimen spillage should be established. All staff should be trained and have to follow protocol. Spill drills should be conducted periodically.

16 An SOP for BSC should be established, which stipulates that before a person leaves the BSC, the arm located in the BSC must be disinfected by spraying with 75% alcohol. All the staff should be trained and assessed according to the SOP.

17 An SOP for nucleic acid extraction should be established. If the nucleic acid preservation solutions do not contain viral inactivators, the specimen tube must be incubated at 56 °C for more than 30 min before extraction, and be kept still for more than 10 min. Subsequently, the tube lid should be opened in the BSC to add specimens, and the testing personnel will conduct biosafety protection at level 2. On the contrary, if the nucleic acid preservation solutions contain viral inactivators, the above control measures do not need to be taken, and only biosafety protection at level 2 is carried out. All the staff should be trained and assessed according to the SOP.

18 An SOP for specimen spillage should be established. All the staff should be trained and assessed according to the SOP. Spill drills should be conducted periodically.

19 An SOP for specimen centrifugation should be established. After the centrifugation, it must be kept still for 10 min, and the lid should be opened in the BSC.

20 An SOP for specimen addition should be established. Regardless of whether the nucleic acid preservation solutions contain viral inactivators, the specimen addition of nucleic acid should be operated in a BSC. All the staff should be trained and assessed according to the SOP.

21 An SOP for specimen spillage should be established. All the staff should be trained and assessed according to the SOP. Spill drills are to be conducted periodically.

22 An SOP for testing fecal specimens should be established, which stipulates that fecal smears should be performed in a BSC, and personnel must wear goggles for biosafety protection at level 2.

23 An SOP for microscopic examination of fecal specimens should be established, which stipulates that the lens and stage of the microscope must be wiped and disinfected with 75% alcohol after each microscopic examination.

24 An SOP for testing fecal specimens should be established, which stipulates that fecal smears should be performed in a BSC; the specimen after testing must be double-packed with sealed bags in a BSC and the surface should be sprayed with 75% alcohol, and subsequently taken out of the laboratory for autoclaving. The smears after microscopic examination should be placed in a glass jar containing 0.2% chlorine-containing disinfectant for immersion and disinfection. All the staff should be trained and assessed according to the SOP.

25 An SOP should be established for the observation of colonies of bacterial cultures, which stipulates that the observation of colonies must be carried out in a BSC, the operators should take the biosafety protection at level 2, and the incubator should be disinfected periodically. All the staff should be trained and assessed according to the SOP.

26 An SOP for waste disposal should be established, which stipulates that the waste generated by nucleic acid testing must be double-packed with sealed bags and subsequently taken out of the BSC for disposal as medical waste. All the staff should be trained and assessed according to the SOP.

27 An SOP for waste disposal should be established, which stipulates that the waste

	generated by culture, identification, and antimicrobial susceptibility test must be double-packed with sealed bags and the surface should be sprayed with 75% alcohol, and subsequently taken out of the laboratory for autoclaving. Sharps, such as pipette tips or glass slides should be placed in a sharps box and then packed with a sealed bag, and then taken out of a BSC for autoclaving. All the staff should be trained and assessed according to the SOP. The disinfection process should be recorded, the disinfection effect should be monitored, and the autoclave should be calibrated periodically (as mentioned in item 4 of Table 3).
28	An SOP for waste disposal should be established, which stipulates that the specimens after testing should be double-packed with sealed bags and then stored in a refrigerator for preservation, and other wastes are to be double-packed with sealed bags and then taken out of the laboratory for disposal as medical waste. All the staff should be trained and assessed according to the SOP.
29	An SOP for specimen storage of nucleic acid of SARS-CoV-2 should be established, which stipulates that the specimens after testing should be covered and placed in a refrigerator with a lock in the clinical biomolecule room, and records should be made.
30	An SOP for microbial specimen storage should be established, which stipulates that the specimens after testing should not be stored. It should be autoclaved on the same day after being double-packed with sealed bags, and the handover records and disinfection records should be made.
31	A fishbone diagram method should be used to identify the risks existing in each test activity. The emergency procedures should be reviewed once a year and be continuously improved by filling gaps through finding the omissions.
32	The system of pre-job training for laboratory staff on emergency procedures should be established and all staff should be assessed. Yearly, the drill plan of emergency procedures should be made, and the drill script should be formulated; subsequently, drills should be carried out and the results of the drills should be summarized.

Notes: The wearing of single-layer latex gloves, work clothing, medical protective masks, and medical work caps is usually regarded as biosafety protection at level 2 in China.

Table 3. Control of laboratory biosafety risks

Discussion

Biosafety assessment includes biosafety identification and evaluation. When implementing biosafety risk assessment, a fishbone diagram method should be used to identify biosafety risks in each test activity. Each test activity involves elements including personnel, equipment, disinfectants, facilities and environment, patient specimens, and operating procedures. These elements should be considered when the biosafety risks are identified. For example, the risk of nucleic acid testing is currently low, owing to the use of nucleic acid preservation solutions containing viral inactivators; however, patients with COVID-19 may be complicated by diarrhea, bacterial or fungal infection of the respiratory tract during hospitalization. In addition to nucleic acid testing, other test activities are also carried out for

patients with COVID-19 in the clinical laboratory of the designated hospitals for treating COVID-19, such as the culture of respiratory specimens and fecal specimens, routine testing of fecal and clinical hematology testing. It is worth noting that the SARS-CoV-2 in specimens of the above test activities are not inactivated before the specimens are sent to the clinical laboratory. Therefore, the laboratory management of designated hospitals for treating COVID-19 should also conduct the biosafety risk assessment and biosafety risk control for these test activities. Meanwhile, as can be seen from our risk assessment results, in addition to the nucleic acid testing of SARS-CoV-2, there are also huge biosafety risks in other test activities.

Biosafety risk assessment and biosafety risk control sometimes need to be repeated many times to improve. Especially for new viruses, since people gradually understand their biological characteristics, the biosafety risk assessment and biosafety risk control also improve accordingly. Therefore, the biosafety risk assessment and biosafety risk control for SARS-CoV-2 we carried out are also based on the gradual understanding of SARS-CoV-2, and we have restarted biosafety risk assessment several times to improve the control measures for biosafety risk.

The most important aspect of biosafety risk assessment is to take appropriate but not excessive control measures for biosafety risk against the risks of different hazard degrees, which can not only reduce the risk to an acceptable range but also save resources and improve the work efficiency. For the same pathogenic microorganism tested in different test activities, the hazard degrees of biosafety risk existing in those test activities are different, and they should be operated in laboratories with different biosafety levels. Therefore, it is

inappropriate to unilaterally emphasize that the biosafety level of the laboratory should be consistent with the hazard level of pathogenic microorganisms tested in the laboratory. For example, the "Biosafety Guideline for Novel Coronavirus Laboratory (Second Edition)" promulgated by the Chinese health authorities stipulates that the virus culture and animal experiments for SARS-CoV-2 must be carried out in laboratories with a biosafety level above P3, while after virus inactivation, the detection activities and personnel biosafety protection are only required to be at level 2.[15] If we use biosafety protection at level 3, which is not based on the specific circumstances, it will not only waste limited medical resources but also reduce the efficiency of work. Especially in the early stages of the epidemic, the specimens after testing or amplified waste were asked for being autoclaved in a nucleic acid laboratory according to experts in China, which led to cross-contamination and the occurrence of nucleic acid false positive events in the laboratory. Chinese health authorities paid attention to such problems and made adjustments immediately, and promulgated the "Organizing and Implementing Guide for Nucleic Acid Testing of Novel Coronavirus for All Personnel (Second Edition)".[16] In addition, the "Laboratory Biosafety Manual (Fourth Edition)" published by WHO abolished the laboratory biosafety level, emphasized the importance of biosafety risk assessment, and the importance of formulating effective but not excessive control measures for biosafety risk according to own economic situation.[6] However, for the same test activity using different types of specimens or different processing methods of specimens, the hazard degrees of the biosafety risks in the test activity are also different. For example, whether the nucleic acid preservation solutions contain viral inactivators, such as guanidine salts and nucleic acid lysates, and whether the virus is inactivated before being

tested, the corresponding biosafety risks in test activities are different. Therefore, protection measures and control measures for biosafety risk should also be formulated according to the risk assessment results. Conclusively, if the nucleic acid preservation solutions containing guanidine salts or nucleic acid lysates are used, or the virus is inactivated after specimen reception, there is a very low biosafety risk in the subsequent test activities, and the biosafety protection at level 2 is sufficient. In addition, Wu et al. reported that the detection rates of SARS-CoV-2 nucleic acid in the blood and fecal specimens were 3.03% and 9.83%, respectively, which were much lower than those of the nasopharyngeal swab and sputum specimens.[17] Therefore, the biosafety risks in the testing process for these four types of specimens are different, and the control measures for biosafety risks to be taken should also be different.

The appropriate control measures for biosafety risk should be formulated to reduce the hazard degree of risk from the two aspects of reducing risk severity and (or) probability of risk occurrence. Meanwhile, it is not necessary to reduce the risk to zero by conducting control measures for biosafety risk, but only to reduce the hazard degree of risk to an acceptable range of laboratory management. On the contrary, excessive control measures for biosafety risk will not only waste limited medical resources but also sacrifice the comfort of personnel and reduce the efficiency of work. Moreover, while considering reducing the hazard degree of biosafety risks, laboratory management should also pay attention to whether control measures will lead to cross-contamination during testing. Therefore, under the current situation of using nucleic acid preservation solutions containing guanidine salts or nucleic acid lysates, laboratory personnel engaged in testing nucleic acid of SARS-CoV-2 are at a

low risk, where there is no need to adopt biosafety protection at level 3 for personnel. Specimens and wastes after testing can be directly transported out of the laboratory as medical waste after being double-packed and sealed without being autoclaved in the nucleic acid laboratory.

At present, although many laboratory management has emphasized biosafety assessment, but ignored biosafety risk management after the assessment. Even if the subsequent test activities or the pathogenic microorganisms exposed to the laboratory personnel had changed, the biosafety risk assessment was not restarted, and the biosafety risk control did not change accordingly. Biosafety risk management is based on self-inspection and dynamic monitoring. The appropriate times for biosafety risk assessment are before test activities are carried out in the laboratory, after the occurrence of biosafety incidents, and when deemed necessary during the risk monitoring process. Biosafety risk monitoring includes monitoring changes in test activity, pathogenic microorganisms involved, monitoring changes in the dose of pathogenic microorganisms used, specimen types, and monitoring for unidentified risks. After the laboratory risk assessment report is formed, risk monitoring is more important. For example, before the outbreak of COVID-19 in China, test activities in clinical laboratories were unlikely to be exposed to SARS-CoV-2. Therefore, biosafety risk assessment did not take into account the biosafety risks posed by SARS-CoV-2, and personnel adopted biosafety protection at level 2. When the COVID-19 epidemic occurred, laboratory management did not realize that the pathogenic microorganisms in the test specimens had changed and might contain SARS-CoV-2. Therefore, the biosafety risk assessment was not restarted, and the control measures for biosafety risk formulated

originally were still used, which led to the infection of laboratory personnel with SARS-CoV-2 in the early stages of the epidemic in Wuhan.[4] In June 2020, viral inactivators were added to all nucleic acid preservation solutions for SARS-CoV-2 in China. The Chinese health authorities subsequently promulgated the biosafety protection standards and workflow for testing nucleic acid of SARS-CoV-2, in which the protection level of nucleic acid testing was reduced. The original protective measures included wearing N95 masks, double-layer latex gloves, goggles, shoe covers, isolation clothing, and protective clothing, which were changed to wearing medical protective masks, single-layer gloves, goggles, isolation clothing, or protective clothing, and shoe covers were optionally worn depending on the situation,[18] which improved comfort and work efficiency.

In addition, laboratory management should review the suitability of laboratory biosafety risk assessment and biosafety risk control on an annual basis and start risk assessment promptly, which is also a part of risk management.

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Conflicts of interest

The authors declare no competing interests.

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